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Bristol-Myers Squibb Company

April 2, 2004

Dockets Management Branch
Food and Drug Administration, HFA-305
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: [Docket No. 2004D-0041] Draft Guidance for Industry on Providing Regulatory Submissions in Electronic Format—Content of Labeling; Federal Register Vol. 69, No. 24, Thursday, February 5, 2004 *(with reference also to the Final Rule **[Docket No. 2000N-1652]** Requirements for Submission of Labeling for Human Prescription Drugs and Biologics in Electronic Format; December 11, 2003; Final Rule - FR Vol. 68, No. 239, page 69009).*

Dear Sir or Madam,

Bristol-Myers Squibb (BMS), a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, infant formulas, and nutritional products, is pleased to have the opportunity to offer comments on the "DRAFT GUIDANCE for Providing Regulatory Submissions in Electronic Format -- Content of Labeling". Our company's mission is to extend and enhance human life by providing the highest-quality pharmaceutical and related health care products. For this reason, we are very interested in commenting on the Draft Guidance of February 5, 2004 and the Final Rule of December 11, 2003.

Summary of BMS Comments on Proposal:

We commend the United States Food and Drug Administration (U.S. FDA) for its effort to implement an electronic document process that would "simplify the drug labeling review process and speed up the approval of labeling changes" as outlined in the Final Rule for the Requirements for Submission of Labeling in Electronic Format. Additionally, we appreciate the FDA's effort to issue this Guidance to provide some clarification for the "Content of Labeling" requirements of the December 11, 2003 Final Rule. We also support FDA's effort to make this document available to the National Library of Medicine for their DailyMed initiative. There are, however, several aspects of the proposed rule and guidance that either appear contrary to the FDA's stated objectives or need some clarification as noted below:

- The relative short timeframe for implementation of Structured Product Labeling (SPL), targeted for December 2004, runs contrary to the statements made in the Final Rule with respect to a reasonable timeframe for introduction of new electronic format for labeling review
- Clarification of the ***content*** for the "Content of Labeling" that will be submitted with the Annual Report
- Clarification for the use of the "Content of Labeling" for a *Special Supplement: Changes Being Effected*
- Clarification of how the SPL will be implemented in the e-CTD format
- Clarification of Quality Control (QC) process that will be used to assure the accuracy of the Content of the SPL in Public Records

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Specific Comments: PDF Format *versus* SPL - Feasibility and Time Frame

BMS notes that the Final Rule identifies the new document as the "Content of Labeling" *(the labeling required under 21 CFR 201.100(d)(3) including all text, tables, and figures [commonly referred to as the package insert or professional labeling]).* We further note that the FDA states that the "Content of Labeling", "at this time", should be in the form of a PDF, the only type of electronic format that FDA can process, review, and archive. However, as per lines 83 to 85 and lines 97 to 104 of the Guidance for the "Content of Labeling" there is a new request for the "Content of Labeling" to be submitted as SPL by December 31, 2004. Although on lines 58 to 60 of the Draft Guidance it did note that the Final Rule stated that "the FDA will periodically issue guidance on how to provide the electronic submission", we did not expect such a major change in format so soon after the Final Rule was issued.

Based on the Final Rule, and *in accordance with FDA's good guidance practice regulations*, BMS understood that the PDF format would not be changed unless sufficient advance notice and time were provided to industry for conversion to any new format or software. Furthermore, the Final Rule stated that any such format or software should be widely available before such a switch would take place because "such changes to the file format or software can lead to costly changes in the information technology systems used by industry". It was also noted that during any such transition, the FDA would accept submissions using the existing file format (PDF), as well as SPL, the newest format recommended by the Agency.

The Draft Guidance, however, states that "it is our goal to complete the transition to SPL format for "Content of Labeling" submissions by the end of 2004". Although the Draft Guidance notes that the FDA would be able to accept the "Content of Labeling" in either PDF or SPL file format, it further states that PDF would be acceptable only until the end of 2004. This proposed rapid transition to SPL raises serious concerns. The proposed SPL format has not yet been validated or tested and is not in wide use by the Pharmaceutical Industry.

BMS, therefore, believes it is premature for the Agency to cite transition goals (i.e., "...by the end of 2004") and to request comment at this time on a concept that is not an approved standard and for which no specific implementation guidance has been provided. While we understand the value of a more granular approach to information exchange ("Content of Labeling" lines 87-95), in the absence of a final standard and a clear understanding of its implementation requirements, it is difficult to fully evaluate the implications of the move to SPL.

BMS is also concerned that this format will not be accepted in all instances and Sponsors will have to provide labeling information in multiple formats to meet the needs of various branches of the Agency. This is not unprecedented, as adverse event reporting is still not standardized across all areas of the Agency. Redundant reporting of adverse events in different formats continues today even though a structured, electronic reporting mechanism has been available for years.

To provide the labeling in SPL format, Sponsors will need to evaluate technical solutions and then test and validate the solution to their own deployment standards. Software to generate an SPL submission is not yet available, and will not be, until sometime after the SPL standard is finalized. Additionally, the Agency needs to understand that budget considerations, as well as the additional human resources, training needs, and process modifications, need to be taken into account before a new technology may be properly implemented at any Company. The Final Rule, let alone the Guidance Document, does not address the additional cost (labor/time/software) required to submit the "Content of Labeling" in SPL format and the proposed timeframe to transition to this format does not seem reasonable, given the current lack of availability of validated software to perform this task.

Recommendation: BMS respectfully requests that the Agency perform an impact/cost analysis on conversion to SPL. In addition, we ask the FDA to determine what the estimated impact would be on the reporting burden for SPL. We also ask that the Agency consider revisiting the timeframe for implementation after the Pharmaceutical Industry and the FDA have an opportunity to become familiar with SPL and its impact on labeling for regulatory submissions (NDAs, ANDAs, SNDAs, BLAs, supplements, and Annual Reports). Furthermore, it should be clearly established that validated and cost effective tools, as well as vendors, be in place to support this effort. It seems apparent that more time will be needed to transition to this new standard before it is made a requirement. BMS suggests that implementation be optional for 1-2 years after the final Guidance is issued to allow proper testing and development of the tools and processes needed to provide this format for all marketed products. We would also like to request that consideration be given to conducting a pilot study with the industry before formal implementation of SPL.

Content* of "Content of Labeling" for the Annual Report** - (21 CFR: §314.81 Other postmarketing reports (b) (2) Annual report (iii) Labeling) - ***Clarification of Text and Information Required For The Annual Report. It was BMS' understanding that the Draft Guidance of February 5, 2004 for the "Content of Labeling" would clarify the *content* in the "Content of Labeling" for various regulatory submissions. However, the Draft Guidance focused exclusively on how to *submit* the "Content of Labeling" in electronic format. The Draft Guidance did not address the contents of the "Content of Labeling".

The Final Rule, therefore, should clarify whether the content should include the most current text *(all approvals, all Special Supplements Changes Being Effected [SSCBE], and all Annual Report changes)* or whether it should only include the text from the package insert that accompanied the marketed product that was implemented during the calendar year, which may or may not match the current labeling.

If FDA wants the "Content of Labeling" to represent the most current text at the time of filing the Annual Report, we would need further clarification as to how this should be presented in the Annual Report. To date, we have identified the differences between labeling used with the marketed product during the specified time frame from that which was submitted the previous year. If the "Content of Labeling" represents the most current labeling, should the Sponsor:

- identify the difference between "Content of Labeling" from that which was used in the marketed product during the specified time frame?
- identify the difference between the "Content of Labeling" from the current year and the "Content of Labeling" from the previous year?

Recommendation: Since the Final Rule is to be implemented by June 8, 2004, BMS would appreciate further clarification from the FDA on what labeling text is to be included as the "Content of Labeling" in the Annual Report and how it should be described.

"Content of Labeling" for a "Special Supplement: Changes Being Effected" (SSCBE)
The Final Rule does not make reference to a *SSCBE (§314.70 Supplements and other changes to approved application (c) Supplements for changes that may be made before FDA approval)* in the ***Changes to Part 314 of the CFR*** (FR 69019). However, the Final Rule does specifically make reference to the "Content of Labeling" in the CFR for other types of submissions (i.e., NDAs, BLAs, ANDAs, and Annual Reports). The omission of a SSCBE from the section identifying changes to the CFR (FR 69019) creates some confusion because the Preamble to the Final Rule does refer to section §314.70 (section V. Paperwork Reduction Act - FR 69015).

Recommendation: BMS requests that FDA clarify whether they want to have a "Content of Labeling" for a SSCBE. Does the reference to "supplements" in the Preamble of the Final Rule address this issue or do we need further clarification in the final Guidance for use of the "Content of Labeling" for a SSCBE. In addition, should a specific reference be added to Part 314 of the CFR (i.e., update to *§314.70)* to address this issue.

Implementation of SPL in the e-CTD format

The Draft Guidance does not provide sufficient information to clearly understand how to organize electronic submissions while utilizing the SPL format. The only information provided is limited to a single line of text (line 152) and a reference to the 1999 eSub Guidances (154 to 157). Draft electronic submission guidances should be aligned with the proposed current submission standards and FDA should provide implementation information for making submissions using the eCTD as well as the older submission standard (eNDA).

Recommendation: BMS would like further clarification on how, and if, the labeling documents defined in the 1999 eSub Guidance (i.e., proposed.pdf, approved.pdf, current.pdf) would be replaced by corresponding SPL XML files. Clarification is requested on how SPL submissions would be made, and negotiations using SPL would take place, regardless of the submission format (eNDA or eCTD). Please provide guidance as to whether FDA anticipates that SPL would replace the Word files now currently used by the FDA in labeling negotiations. The process for the exchanging of labeling information should be well defined. Further, clarification is needed on how labeling changes would be communicated using the SPL format when there are multiple pending supplements.

Responsibility for QC of the Content of the SPL in Public Records

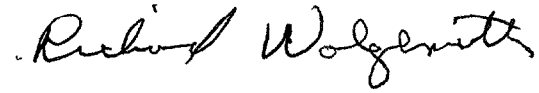
It is suggested in this Guidance document *(line 68 - 73)* that the SPL format "...will be used to support health information management technologies such as electronic prescribing and the electronic health record (EHR)." While BMS supports these initiatives, we are concerned that the use of SPL increases the possibility of technology failure, which may jeopardize the integrity of the information provided to the public. While there certainly are potential issues in disseminating information to the public using the current PDF format, these are limited and the Sponsor bears the burden of QC of those rendered PDF files. The additional variations brought about by content interpretation, transformation, and style sheet presentation as a result of XML technology should also be a concern to the Agency, as well as the Sponsors.

Recommendation: BMS would appreciate additional information as to how this technology will be quality assured to ensure that labeling information disseminated to the public will represent the most current and up-to-date information available from the sponsor.

Conclusion:

BMS appreciates the opportunity to provide comment and respectfully requests that FDA give consideration to our recommendations.

Sincerely,



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